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Evaluation of tumor burden after sequential molecular-targeted therapy in patients with metastatic renal cell carcinoma

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Running title

TB during sequential TT in mRCC patients

Words

Abstract 242 words Manuscript text 2235 words

Abstract

Background: To evaluate the effect of tumor burden (TB) on survival in patients with metastatic renal cell carcinoma (mRCC) who are administered sequential molecular-targeted therapy (TT).

Methods: Sixty-eight patients were recruited. Baseline TB at the time of second-line TT initiation was calculated according to the Response Evaluation Criteria in Solid Tumors v. 1.1. Patients were divided into 2 subgroups according to the median TB: greater than the median as the high group, lower than the median as the low group. Progression-free survival (PFS) and overall survival (OS) after second-line therapy were analyzed. The effect of TB changes on survival during sequential TT were also evaluated.

Results: Median second-line TB was 57.7 cm. The patients with high TB had significantly poorer PFS and OS, compared to those with low TB (median PFS, 4.36 vs. 8.19 months, $p = 0.0119$; OS, 9.6 vs. 23.5 months, $p = 0.0107$). For PFS, multivariate analyses revealed that second-line objective response was an independent predictor ($p < 0.0001$), but second-line TB was not ($p = 0.0826$). For OS, second -line TB and objective response were independent predictors ($p = 0.0300$ and < 0.0001, respectively). Moreover, there was a positive correlation

between first- and second-line TB (r^2 = 0.460, p < 0.0001), although TB changes between first- and second-line therapies did not affect survival (median PFS, p = 0.812; OS, p = 0.415).

Conclusions: Second-line TB was an independent predictor of OS among patients with mRCC after second-line TT.

Mini-abstract

Second-line tumor burden was an independent predictor of overall survival among patients with metastatic renal cell carcinoma after second-line molecular-targeted therapy.

Key words

Tumor burden, second-line, molecular-targeted therapy, metastatic renal cell carcinoma, predictor, biomarker

Introduction

Molecular-targeted agents for the treatment of metastatic renal cell carcinoma (mRCC) have been developed. Compared with cytokine therapy, these new drugs have significantly improved prognosis in patients with mRCC (1, 2). Because of improvements in response, numerus investigations into potential predictors or biomarkers of survival have been conducted, and prognostic models have been described to help to stratify the risks of disease progression or death (3). In this context, imaging findings, according to the standard Response Evaluation Criteria in Solid Tumors (RECIST) (4), have been identified as objective and effective prognostic indictors. Lacovelli et al. (5) suggested that tumor burden (TB), which was defined as the sum of the longest unidimensional diameter of each target lesion (restricted to axial CT), at the time of first-line molecular-targeted therapy (TT) initiation was an independent prognosticator of survival in patients with mRCC. However, for sequential TT, the effect of TB on prognosis in patients with mRCC is unknown. Moreover, Lacovelli et al. (5) included patients who had received prior cytokine therapy (6, 7). Therefore, to the best of our knowledge, there are limited studies that have investigated the effect of TB on survival during sequential TT in patients who have not undergone prior

cytokine therapy.

Thus, the aim of this study was to evaluate the predictive role of second-line TB on survival among mRCC patients who underwent second-line TT without prior cytokine therapy. Moreover, the influence of TB changes during sequential TT on survival was investigated.

Patients and methods

Patients and study design

The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 3942), which was performed in accordance with the principals outlined in the Declaration of Helsinki.

In our department, 120 patients underwent second-line targeted therapy (37 were administered sunitinib; 3, sorafenib; 4, pazopanib; 43, axitinib; 11, temsirolimus; and 22, everolimus) between January 2008 and March 2016. Among these, 29 patients who underwent prior cytokine therapy, 7 patients who underwent dialysis therapy, and 11 patients who experienced adverse events during first-line therapy were excluded. For the remaining 76 patients, 8 patients whose clinical (n = 4) or imaging (n = 4) data were not available were also

excluded. Finally, 68 patients (19 were administered sunitinib; 2, sorafenib; 3, pazopanib; 32, axitinib; 4, temsirolimus; and 8, everolimus) were enrolled in this retrospective study (Figure 1). Clinical and laboratory data were obtained from the electronic database and patient medical records.

Imaging methods and imaging evaluation

Baseline imaging examinations, including plain or contrast-enhanced CT or MRI of the chest, abdomen, and pelvis were performed within 28 days before the start of a new therapy. The target lesions were selected based on the baseline imaging results, and were evaluated according to RECIST v. 1.1 (4) i.e., a maximum of 5 lesions, with a maximum of 2 per organ per patient. Lymph nodes were only selected as target lesions if the short axis was longer than 15mm. Sclerotic osseous lesions were excluded. Two investigators (HI and TK), who were blinded to all other clinical parameters and outcomes, performed the image analyses.

Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U*-test, and categorical variables were analyzed using the χ^2 test. To evaluate the influence

of second-line TB on patient outcomes, patients were divided into 2 subgroups according to the TB value as higher than the median (high group) or lower than the median (low group). Progression-free survival (PFS) and overall survival (OS) after second-line therapy were compared between the groups using the Kaplan-Meier method and the log-rank test. PFS was defined as the time of second-line therapy initiation to the date of progression or death from any cause. OS was defined as the time of second-line therapy initiation to death from any cause. Univariate and multivariate analyses using Cox proportional hazards regression models were used to identify factors that were associated with PFS and OS. First- and second-line TB were calculated for each patient and first-line TB was plotted against second-line TB on a scatter plot. Pearson's correlation coefficient was used to compare first- and second-line TB. To evaluate the influence of TB changes on survival, the correlation between first- and second-line TB at the time of treatment initiation was evaluated by dividing patients into three subgroups according to the ratio of second-line to first-line TB (i.e., [second-line TB – first-line TB]/first-line TB): Group A: ≥ 0.2, Group B: ≤ -0.2, and Group C: between -0.2 and 0.2. PFS and OS were compared among the three groups. Survival risk was expressed as hazard ratios (HR) and 95% confidence intervals (CIs). All

analyses were performed using JMP software (version 11; SAS Institute Inc., Cary, NC, USA), and a *p*-values of <0.05 was considered statistically significant.

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. The mean age was 64.3 years (median, 67.5 years; range 29–87 years). Second-line Memorial Sloan Kettering Cancer Center (MSKCC) risk classification was identified according to Motzer's risk classification (8).

Survival according to second-line tumor burden

Figure 2 shows the Kaplan-Meier survival curves of PFS and OS after second-line therapy according to second-line TB. The patients with high TB had significantly lower PFS and OS, compared to the patients with low TB (median PFS, 4.36 vs. 8.19 months, $p = 0.0119$; OS, 9.6 vs. 23.5 months, $p = 0.0107$).

Survival according to first-line tumor burden

Figure 3 shows the Kaplan-Meier survival curves of first-line PFS and OS after

first-line therapy according to first-line TB. Similar to second-line, patients were divided into two subgroups according to TB value: higher than the median (high group) or lower than the median (low group). The OS rate was significantly lower in patients with high TB compared to those with low TB (median, 20.6 vs. 43.8 months, $p = 0.0091$), whereas PFS did not significantly differ between the two groups (median, 7.91 vs 8.43 months, $p = 0.193$).

Predictors of survival

On univariate analysis, significant predictors of PFS were second-line MSKCC, pathology, second-line TB, and objective response (OR) (all, $p < 0.05$). On multivariate analysis, for PFS, second-line OR was an independent predictor ($p < 0.0001$) (Table 2). On univariate analysis, significant predictors of OS were second-line MSKCC, pathology, first-line agent, second-line TB, and OR (all, $p < 0.05$). On multivariate analysis, for OS, second-line TB and OR were independent predictors (HR 1.01, $p = 0.0207$; and $p < 0.0001$, respectively) (Table 3).

Impact of tumor burden changes on survival during sequential molecular-targeted therapy

Figure 4 shows that there was a positive correlation between first- and second-line TB (r^2 = 0.460, p < 0.0001), Moreover, according to subgroup classification based on the TB changes from first- to second-line therapy, 29 (42.6%), 19 (27.9%), and 20 (29.4%) patients were categorized in Groups A, B, and C, respectively. Figure 5 shows that there were no significant differences in PFS and OS between the groups (median PFS, 7.2, 6.84, and 5.96 months, p = 0.812; OS, 13.2, 11.1, and 23.5 months, p = 0.415 in Groups A, B, and C, respectively).

Discussion

The present study revealed that second-line TB was an independent predictor of OS but not PFS after second-line TT among patients with mRCC who did not undergo prior cytokine therapy. There was also a significant correlation between first- and second-line TB, although TB changes during sequential TT did not significantly affect PFS or OS. To the best of our knowledge, this is the first study to evaluate TB during sequential TT in patients with mRCC who did not undergo prior cytokine therapy.

TB has been suggested as a useful prognosticator in many malignancies. With regard to renal cancers, its role in predicting survival has been previously

identified (5). Using clinical data from previous prospective trials, Lacovelli et al. (5) first identified the influence of TB on mRCC patient survival at the time of first-line TT initiation (5). According to that study, after the patients were divided into 3 subgroups based on TB values, there were significant differences in the first, second, and third tertile of PFS and OS, and TB (per 1cm-increase) was a prognostic factor for PFS and OS. However, some patients in their cohort had undergone prior cytokine therapy. In clinical practice, TT is a current treatment strategy for mRCC (9, 10), but data from patients who had not undergone prior cytokine therapy is lacking. Moreover, OR to second-line TT was not evaluated in the previous study (5). OR is a useful prognosticator in mRCC patients during TT (11-13), and in the present analysis second-line TB and OR were independent prognosticators of OS. We believe that these results are important for predicting prognosis in mRCC patients undergoing TT because OR is a strong predictor of outcome. However, second-line OR cannot be evaluated prior to treatment, whereas second-line TB can be easily evaluated prior to second-line TT initiation. Therefore, the present study shows that both second-line TB and OR, according to imaging findings, can effectively predict patient prognosis and improve treatment strategies for mRCC.

We also found that first-line TB was associated with OS, suggesting that TB was a useful predictive factor for OS with both first- and second-line therapy. Meanwhile, first-line PFS was not associated with TB. In addition, as reported by Lacovelli et al. (5), the Kaplan-Meier PFS curve between the first- and second-tertiles showed no difference, although the multivariate analysis showed a significant influence of TB on PFS. Thus, the impact of TB as a predictor for PFS may remain controversial.

Previous studies have suggested that TB was a significant predictive marker of malignant potential not only for metastatic lesions but also for primary renal lesions. In a cohort of 2770 patients who underwent surgery for localized renal tumors, Frank et al. (14) demonstrated that as tumor size increased there was a significant increase in the proportion of clear-cell carcinoma and high grade malignancy in renal tumors. Similarly, Thomson et al. (15) demonstrated that each 1cm-increase in renal tumor size was associated with a 16% increase in the risk for malignancy, and for patients with clear-cell carcinoma, each 1cm-increase in tumor size increased the risk of a high-grade tumor. They also suggested that primary tumor size was significantly associated with the risk of synchronous metastasis and inferior metastases-free survival in patients with non-metastatic

RCC (16).

The present study found that there was significantly relativity between first- and second-line TB. This is congruent with the findings of a previous study. In patients with mRCC undergoing tyrosine kinase inhibitor treatment, Yuasa et al. (17) found that the magnitude of tumor shrinkage depended on the initial TB. According to their study, a higher initial tumor volume and poorer tumor shrinkage resulted in a higher tumor volume at the time of second-line therapy initiation. However, TB changes between first- and second-line therapies did not influence patient outcome. In other words, the magnitude of tumor shrinkage during first-line therapy did not affect second-line survival, suggesting a lack of correlation between first-line PFS and second-line survival (11, 18). Our previous study in mRCC patients undergoing sequential TT indicated that neither the magnitude of tumor shrinkage during first-line therapy nor first-line PFS were associated with second-line PFS or OS (12). Moreover, several previous studies suggested that there was no correlation between first- and second-line vascular endothelial growth factor inhibitor (VEGFi) treatment, and that the clinical response to a second-line VEGFi was not dependent on response to the first-line VEGFi (19, 20). Therefore, the results of the present study are consistent with those of

previous studies.

Finally, this study may support the indication of a new drug (programmed death-1 (PD-1) checkpoint inhibitor: nivolumab) as a second-line agent. A previous pivotal randomized trial demonstrated the efficacy of this drug in cohorts of patients with mRCC who had received one or two previous regimens of antiangiogenic therapy (21). As patients with high TB have poor prognoses, even after initiation of second-line TT consisting of conventional agents, we may need to treat such high-risk patients with nivolumab. However, the association between TB and nivolumab remains unclear, and this suggestion should be confirmed in future investigations.

The present study had several limitations. First, this study was performed retrospectively in a single-center with small cohort; therefore, there may be unavoidable patient selection bias. Second, during the follow-up period, the strategy of sequential TT was inconsistent. Recently sequential TT in our institute consisted of first-line sunitinib and second-line axitinib, however, in previous era, because of lack of TT approval, different regimens were used. For example, before sunitinib was approved (prior to 2008), sorafenib was administered as a first-line agent, and before axitinib was approved (prior to 2012), temsirolimus or

everolimus was administered as a second-line agent. Moreover, in several cases of non-clear cell carcinoma, or high risk based on MSKCC classification, temsirolimus rather than tyrosine kinase inhibitors was used as a first-line agent (10). However, multivariate analysis including factors such as pathology, MSKCC classification, and targeted agents was performed to remove selection bias as much possible. Therefore, the findings of the present study should be confirmed in a prospective study with a large and homogenous patient cohort.

In conclusion, the present study revealed that second-line TB was an independent predictor of second-line OS among patients who underwent sequential TT without prior cytokine therapy. Moreover, we found that there was significant correlation between first- and second-line TB, whereas TB changes between first- and second-line therapies did not affect PFS or OS. Our results, based on imaging examination prior to second-line therapy initiation, might enable more effective prognosis prediction and improve mRCC treatment strategies. Moreover, when shifting to second-line therapy, it might not be necessary to consider the clinical response during first-line therapy.

Conflict of interest statement

The authors have no financial interests or potential conflicts of interest.

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Figure legends

Figure 1: Patient selection

SU, sunitinib; SO, sorafenib; PA, pazopanib; AX, axitinib; TE, temsirolimus; EV, everolimus

Figure 2: Patient survival according to second-line tumor burden

The patients were classified into two groups according to second-line TB; 34 patients were classified into the high TB group (≥ 57.7 cm), and the remaining 34 patients were classified into the low TB group (< 57.7 cm). The PFS and OS rates were calculated using the Kaplan-Meier method and were compared using the log-rank test (PFS, $p = 0.0119$; OS, $p = 0.0107$).

TB, tumor burden; PFS, progression-free survival; OS, overall survival

Figure 3: Patient survival according to first-line tumor burden

The patients were classified into two groups according to first-line TB; 34 patients were classified into the high TB group (≥ 47.0 cm), and the remaining 34 patients were classified into the low TB group (< 47.0 cm). The PFS and OS rates were calculated using the Kaplan-Meier method and were compared using the log-rank test (PFS, $p = 0.193$; OS, $p = 0.0091$).

TB, tumor burden; PFS, progression-free survival; OS, overall survival

Figure 4: Correlation of tumor burden between first- and second-line therapies

Pearson's correlation coefficient analysis showed that there was a positive correlation between first- and second-line TB ($r^2 = 0.460$, $p < 0.0001$).

TB, tumor burden

Figure 5: Patient survival according to tumor burden changes between first- and second-line therapies

The PFS and OS rates were calculated using the Kaplan-Meier method and compared using the log-rank test (PFS, $p = 0.812$; OS, $p = 0.415$). TB changes were calculated as follows: (second-line TB – first-line TB)/first-line TB.

PFS, progression-free survival; OS, overall survival, TB; tumor burden

Table 1: Patient background

Variable	Number (n = 68)
Age at second-line therapy initiation (years)	
≥ 65	41 (60.3%)
< 65	27 (39.7%)
Sex	
Male	45 (66.2%)
Female	23 (33.8%)
First-line MSKCC	
Favorable	10 (14.7%)
Intermediate	48 (70.6%)
Poor	10 (14.7%)
Second-line MSKCC	
Favorable	6 (8.82%)
Intermediate	41 (60.3%)
Poor	21 (30.9%)
Prior nephrectomy	
Yes	64 (94.1%)

No	4 (5.88%)
Pathology	
Clear cell carcinoma	48 (70.6%)
Non-clear cell carcinoma	20 (29.4%)
Clear cell carcinoma with spindle	4 (5.88%)
Papillary renal cell carcinoma type 2	11 (16.2%)
Mucinous tubular and spindle cell carcinoma	1 (1.47%)
Medullary carcinoma	1 (1.47%)
Unknown	3 (4.41%)
First-line agent	
TKI	60 (88.2%)
Sunitinib	36 (52.9%)
Sorafenib	21 (30.9%)
Pazopanib	3 (4.41%)
mTORi	8 (11.8%)
Temsirolimus	7 (10.3%)
Everolimus	1 (1.47%)

Second-line agent	
TKI	56 (82.3%)
Sunitinib	19 (27.9%)
Sorafenib	2 (2.94%)
Pazopanib	3 (4.41%)
Axitinib	32 (47.1%)
mTORi	12 (17.6%)
Temsirolimus	4 (5.88%)
Everolimus	8 (11.8%)
Metastatic organs	
Lung	29 (42.6%)
Liver	10 (14.7%)
Bone	7 (10.3%)
Lymph nodes	18 (26.5%)
Others	12 (17.6%)
First-line tumor burden (cm)	69.2 (47.0, 10 – 427)
Second-line objective response	
Complete response	1 (1.47%)

Partial response	11 (16.2%)
Stable disease	41 (60.3%)
Progression disease	15 (22.1%)
Second-line tumor burden (cm)	82.6 (57.7, 10.6 – 313)
Disease progression	
Yes	54 (79.4%)
No	14 (20.6%)
Death from any cause	
Yes	43 (63.2%)
No	25 (36.8%)
Follow-up period (months)	14.2 (10.5, 1.81 – 50.7)

MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Table 2: Univariate and multivariate analyses for second-line PFS

Variable	Univariate HR (95%CI)	*p*	Multivariate HR (95%CI)	*p*
Age		0.354		
≥ 65	Reference			
< 65	1.30 (0.74 – 2.23)			
Sex		0.400		
Male	Reference			
Female	1.27 (0.72 – 2.21)			
First-line MSKCC		0.803		
Favorable/intermediate	Reference			
Poor	1.11 (0.45 – 2.33)			
Second-line MSKCC		0.0021		0.100
Favorable/intermediate	Reference		Reference	
Poor	2.69 (1.45 – 4.87)		1.72 (0.90 – 3.25)	
Pathology		0.0006		0.112
CCC	Reference		Reference	
Non-CCC	2.98 (1.63 – 5.30)		1.72 (0.88 – 3.30)	

First-line agent TKI mTORi	 Reference 1.67 (0.73 – 3.37)	0.212		
Second-line agent TKI mTORi	 Reference 1.53 (0.77 – 2.85)	0.216		
Second-line objective response Complete and partial response Stable disease Progression disease	 0.30 (0.11 – 0.68) Reference 27.8 (9.76 – 92.7)	<0.0001 0.0031 - <0.0001	 0.39 (0.14 – 0.94) Reference 25.9 (8.78 – 89.3)	<0.0001 0.0364 - <0.0001
Second-line tumor burden	1.01 (1.00 – 1.01)	0.0006	1.00 (1.00 – 1.01)	0.0826

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Table 3: Univariate and multivariate analyses for second-line OS

Variable	Univariate HR (95%CI)	*p*	Multivariate HR (95%CI)	*p*
Age		0.179		
≥ 65	Reference			
< 65	1.52 (0.82 – 2.80)			
Sex		0.345		
Male	Reference			
Female	1.35 (0.72 – 2.49)			
First-line MSKCC		0.267		
Favorable/intermediate	Reference			
Poor	1.70 (0.63 – 3.88)			
Second-line MSKCC		0.0004		0.109
Favorable/intermediate	Reference		Reference	
Poor	3.37 (1.76 – 6.32)		1.89 (0.86 – 3.98)	
Pathology		0.0013		0.725
CCC	Reference		Reference	
Non-CCC	3.06 (1.58 – 5.75)		1.16 (0.51 – 2.54)	

First-line agent		0.0085		0.0940
TKI	Reference		Reference	
mTORi	3.34 (1.40 – 7.14)		2.33 (0.86 – 5.97)	
Second-line agent		0.557		
TKI	1.24 (0.61 – 2.76)			
mTORi	Reference			
Second-line objective response		<0.0001		<0.0001
Complete and partial response	0.28 (0.08 – 0.72)	0.0066	0.38 (0.10 – 1.09)	0.0743
Stable disease	Reference	-	Reference	-
Progression disease	8.48 (3.56 – 19.9)	<0.0001	7.93 (3.07 – 20.6)	<0.0001
Second-line tumor burden	1.01 (1.00 – 1.01)	0.0002	1.01 (1.00 – 1.01)	0.0300

OS, overall survival; HR, hazard ratio; CI, confidence interval; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor

Figure 1

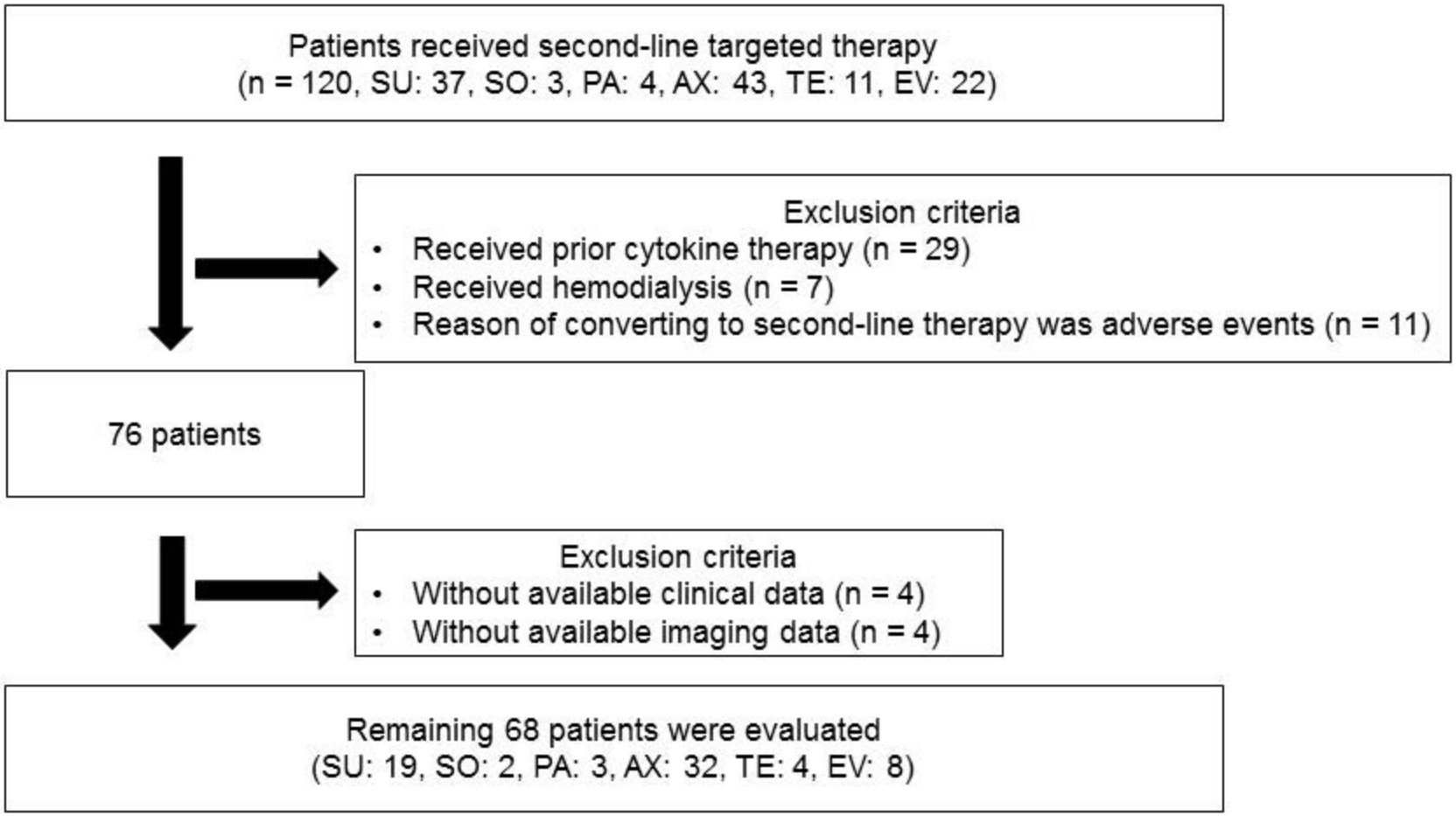
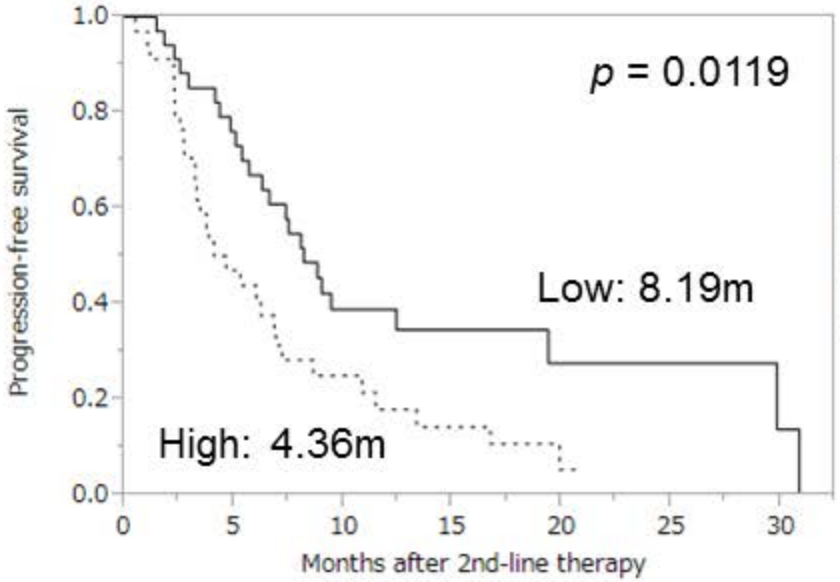

Patients received second-line targeted therapy
(n = 120, SU: 37, SO: 3, PA: 4, AX: 43, TE: 11, EV: 22)
Exclusion criteria
• Received prior cytokine therapy (n = 29)
• Received hemodialysis (n = 7)
• Reason of converting to second-line therapy was adverse events (n = 11)
76 patients
Exclusion criteria
• Without available clinical data (n = 4)
• Without available imaging data (n = 4)
Remaining 68 patients were evaluated
(SU: 19, SO: 2, PA: 3, AX: 32, TE: 4, EV: 8)

Figure 2


Progression-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Months after 2nd-line therapy
p = 0.0119
Low: 8.19m
High: 4.36m

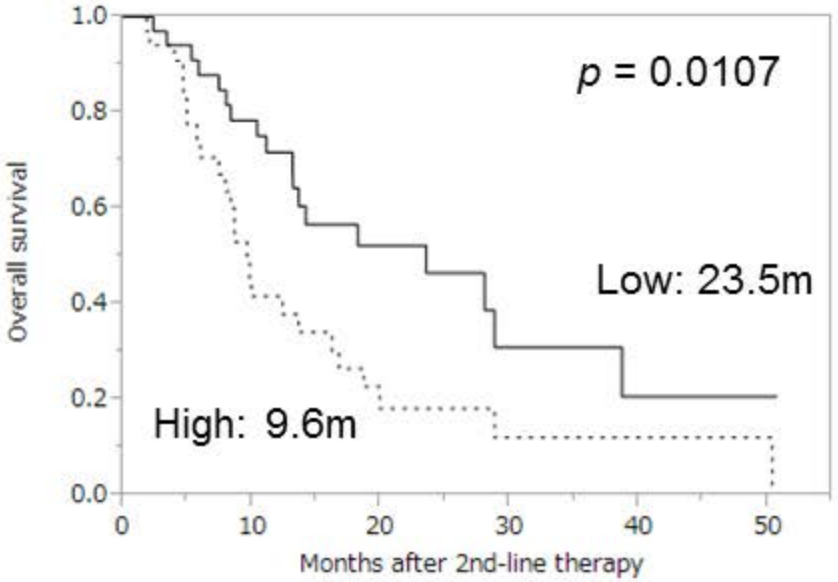
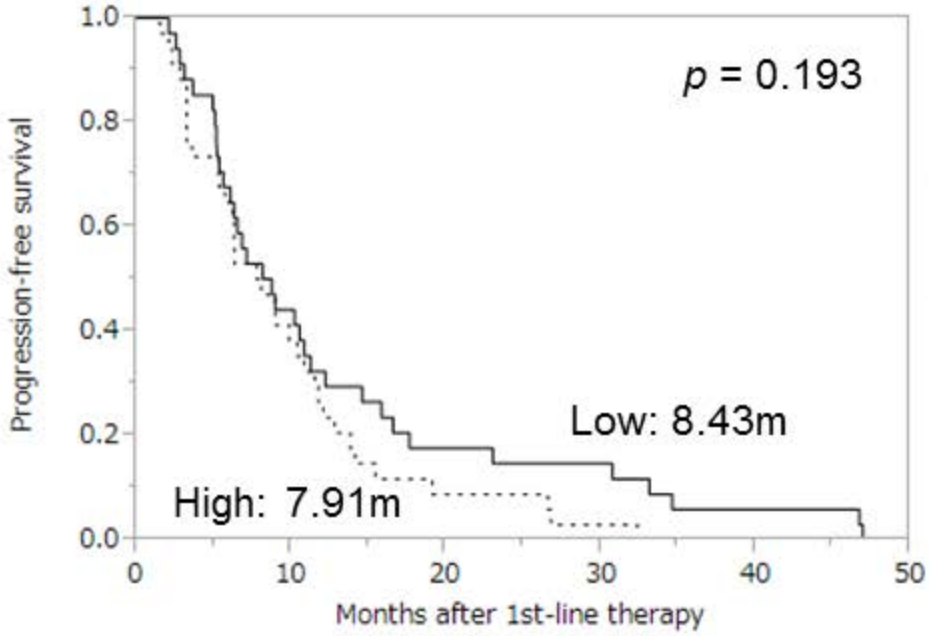

Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Months after 2nd-line therapy
p = 0.0107
Low: 23.5m
High: 9.6m

Figure 3


1.0
0.8
0.6
0.4
0.2
0.0
Progression-free survival
p = 0.193
Low: 8.43m
High: 7.91m
0
10
20
30
40
50
Months after 1st-line therapy

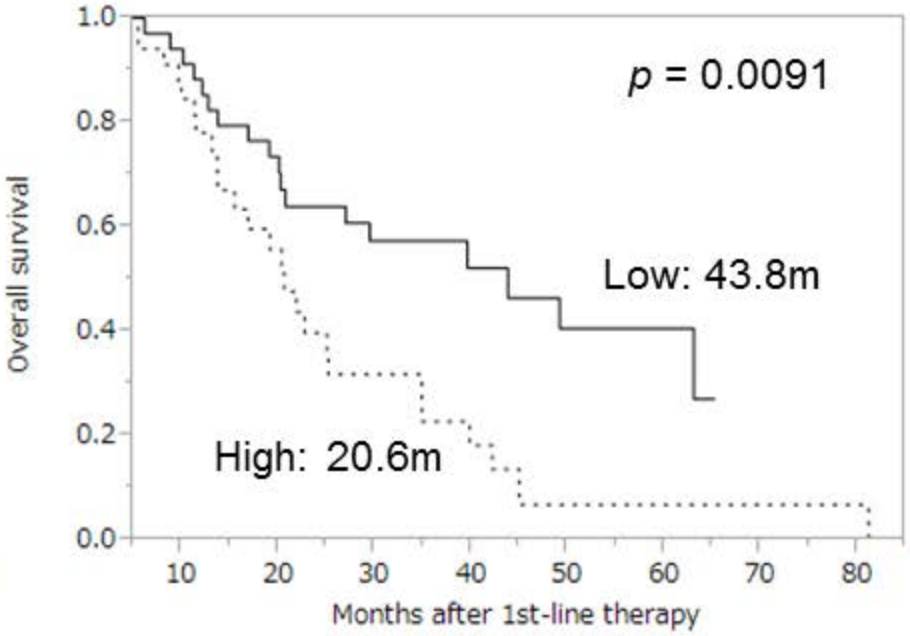

1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
p = 0.0091
Low: 43.8m
High: 20.6m
10
20
30
40
50
60
70
80
Months after 1st-line therapy

Figure 4

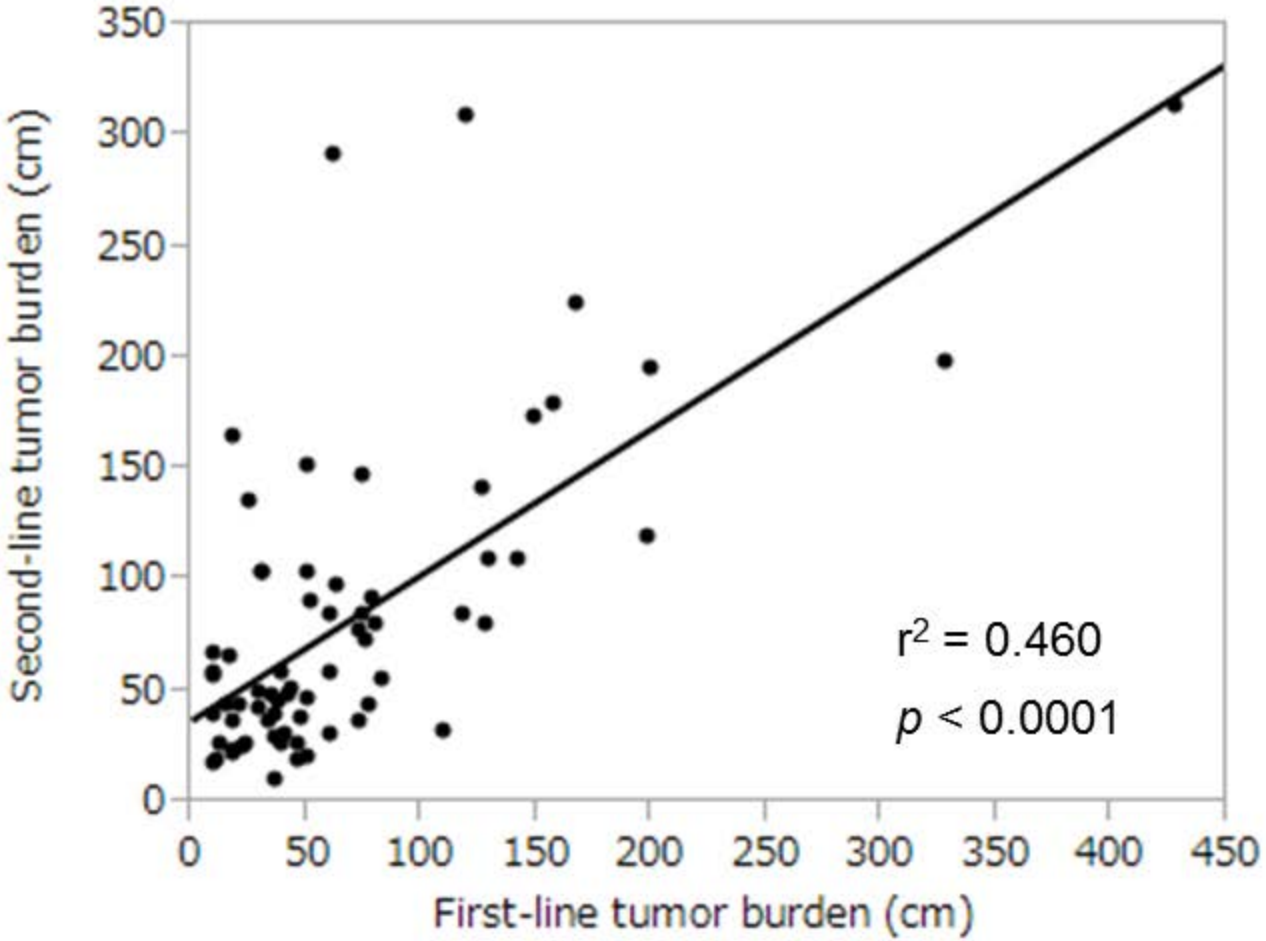
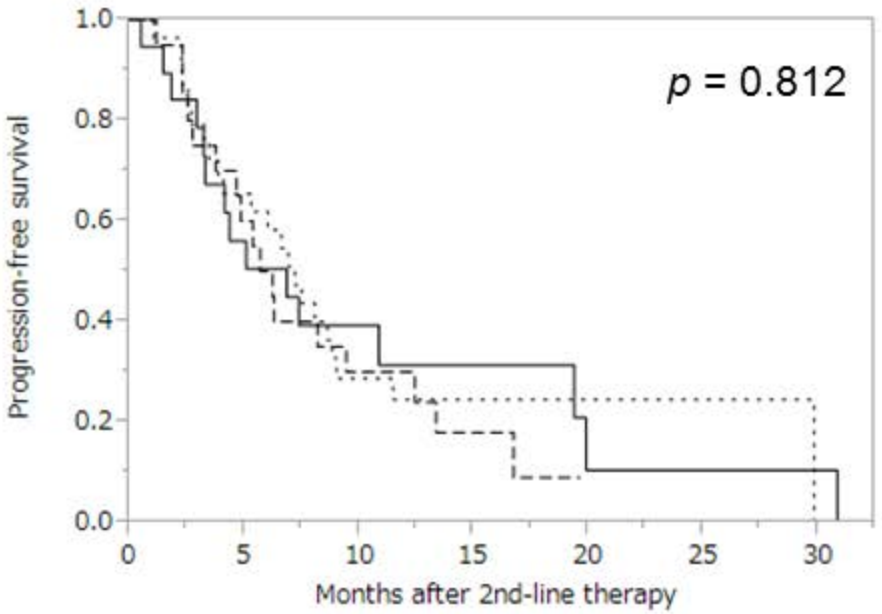
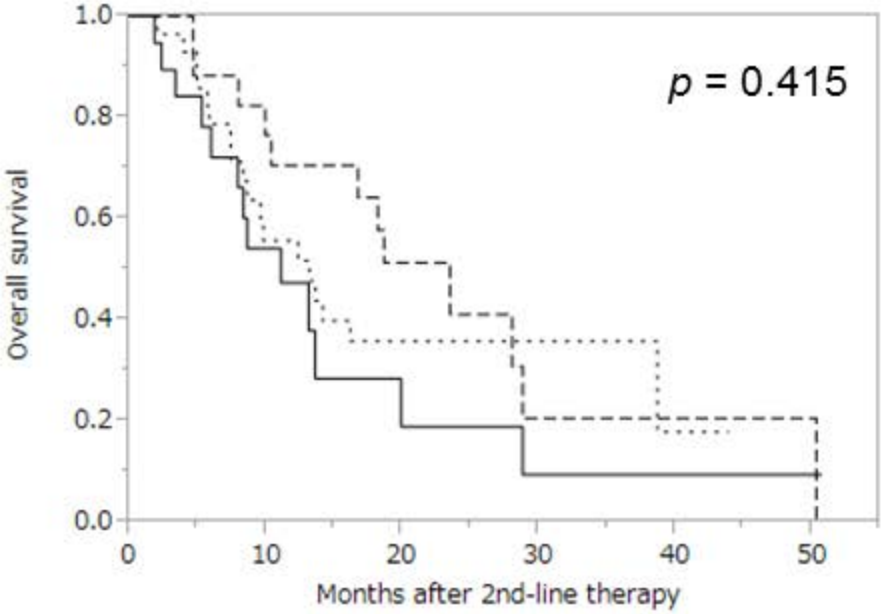

Second-line tumor burden (cm)
First-line tumor burden (cm)
0
50
100
150
200
250
300
350
400
450
r² = 0.460
p < 0.0001

Figure 5





Group	Median PFS (month)	Median OS (month)
A (n = 29)	7.2	13.2
B (n = 19)	6.84	11.1
C (n = 20)	5.96	23.5